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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/532,831
Filing Date: March 09, 2006
Appellant(s): PETEREIT ET AL.

Daniel Pereira
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 3, 2010 appealing from the Office action mailed November 4, 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1 - 3, 8 – 11, 13, 14 and 16 are pending. As claims 10 and 11 are withdrawn from consideration, claims 1 – 3, 8, 9, 13, 14 and 16 are rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

US 5643602	ULMIUS et al.	7-1997
WO 01/68058	BECKERT et al.	9-2001
US 2002/0192282	BECKERT et al.	12-2002

Gang et al. Proceedings of the 7th SCEJ, p 165 – 169, 2001.

Knop, European Journal of Pharmaceutical Sciences, 4, p 293-300, 1996.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1 – 3, 8, 9, 13, 14 and 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ulmius et al. (US 5,643,602) in view of Beckert et al. (WO 01/68058, citations from the English equivalent US 2002/019228).

Ulmius discloses multilayer compositions of corticosteroids such as budesonide (col 3, ln 6; col 4, ln 50). Each unit comprises a core and two layers on that core (col 5, ln 3 – 4). The core can either be formulated with the glucocorticosteroid homogenously throughout the core or the active ingredient can be applied to the exterior of the seed (col 5, ln 5 – 8). When the drug is applied to the seed, the drug is applied in combination with a polymer that acts as a binder for the active ingredient and to limit the release rate (col 5, ln 12 – 16). Preferred film-forming polymers are ethylcellulose or copolymers of acrylic and methacrylic acid esters such as the compounds sold under the tradenames EUDRAGIT® NE, EUDRAGIT® RL and EUDRAGIT® RS (col 5, ln 24 – 26). EUDRAGIT® NE 30D is a polymer that meets the monomer requirements for the inner coating in claims 1 and 2 as it contains 65 wt% ethyl acrylate and 35% wt% methyl methacrylate (p 26, ln 10 – 12 of the instant application). The ratio of the active ingredient to the polymer is 1:6.6 and 1:2.4 examples 1 and 2 respectively (col 8, ln 24 – 30; col 9, ln 14 – 20). The film-forming temperature of the polymer is determined by the composition of the polymer and as the composition of the polymers are the same, the

film-forming temperature of the polymer will meet the limitations set forth in the claim. The release profile of the active ingredient should be such that no release occurs in the stomach but is released in either the small intestine or caecum (col 4, ln 34 – 40) so that the active ingredient reaches the inflamed portion of the bowel at a sufficient concentration to exert its local action (col 4, ln 44 – 49). The coatings may optionally comprise plasticizers or release agents (anti-adhesives; col 5, ln 48 – 51).

Ulmius et al. does not discloses a combination of EUDRAGIT® NE 30 D with a polymer recited in subitem c) of claim 1, such as EUDRAGIT® FS (see p 21, ln 16 – 18 of instant specification) or any other active ingredients besides glucocorticosteroids as suitable for use in such compositions.

Beckert et al. discloses a multilayer drug form with a core and both an inner and outer polymer coatings (¶ [0001]). This dosage form is designed to release virtually no active ingredient in the stomach and have a uniform, long-lasting release of the active ingredient to both the small intestine and colon (¶ [0006]). A number of active ingredients are suitable for use in these compositions, including budesonide (paragraph [0043]), but also aminosalicylates such as 5-aminosalicyclic acid, sulfonamides and glucocorticosteroids (¶¶ [0032] – [0034]). Beckert et al. discloses that a particularly suitable polymer for the outer coating of the multilayer pharmaceutical formulation is a (meth)acrylate copolymer composed of 10 – 30 wt% methyl methacrylate, 50 to 70 wt% methyl acrylate and 5 to 15 wt% methacrylic acid (EUDRAGIT® FS type; ¶ [0087]).

It would have been obvious to one of ordinary skill in the art to replace the budesonide designed for delivery to the small intestine and/or colon in the multilayer

dosage form taught by Ulmius with other active agents such as 5-aminosalicylate that are also targeted for the small intestine and colon as taught by Beckert et al. It also would have been obvious to use a EUDRAGIT® FS type polymer as the outer coating and the ethyl acrylate and methyl methacrylate copolymer for the inner coating in the multilayer dosage form as both Ulmius and Beckert et al. teach multilayer dosage forms with a core and two coating layers that release virtually no active substance in the stomach and deliver the active agent to the small intestine or colon. While the multilayer dosage form of Beckert et al. contains the active ingredient in the core, Ulmius discloses that the active ingredient can either be included in the core or in the first layer that is coated onto that core.

Claims 1 – 3, 8, 13, 14 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulmius et al. (US 5,643,602) in view of Gang et al. (Proceedings of the 7th SECJ, 2001; cited on IDS submitted July 23, 2009).

Ulmius discloses multilayer compositions of corticosteroids such as budesonide (col 3, ln 6; col 4, ln 50). Each unit comprises a core and two layers on that core (col 5, ln 3 – 4). The core can either be formulated with the glucocorticosteroid homogenously throughout the core or the active ingredient can be applied to the exterior of the seed (col 5, ln 5 – 8). When the drug is applied to the seed, the drug is applied in combination with a polymer that acts as a binder for the active ingredient and to limit the release rate (col 5, ln 12 – 16). Preferred film-forming polymers are ethylcellulose or copolymers of acrylic and methacrylic acid esters such as the compounds sold under the tradenames

EUDRAGIT® NE, EUDRAGIT® RL and EUDRAGIT® RS (col 5, ln 24 – 26). EUDRAGIT® NE 30D is a polymer that meets the monomer requirements for the inner coating in claims 1 and 2 as it contains 65 wt% ethyl acrylate and 35% wt% methyl methacrylate (p 26, ln 10 – 12 of the instant application). The ratio of the active ingredient to the polymer is 1:6.6 and 1:2.4 examples 1 and 2 respectively (col 8, ln 24 – 30; col 9, ln 14 – 20). The film-forming temperature of the polymer is determined by the composition of the polymer and as the composition of the polymers are the same, the film-forming temperature of the polymer will meet the limitations set forth in the claim. The release profile of the active ingredient should be such that no release occurs in the stomach but is released in either the small intestine or caecum (col 4, ln 34 – 40) so that the active ingredient reaches the inflamed portion of the bowel at a sufficient concentration to exert its local action (col 4, ln 44 – 49). The coatings may optionally comprise plasticizers or release agents (anti-adhesives; col 5, ln 48 – 51).

Ulmius et al. does not discloses a combination of EUDRAGIT® NE 30 D with a polymer recited in subitem c) of claim 1, such as EUDRAGIT® FS.

Gang et al. discloses a colon specific delivery system which consists of a tablet core and double coating film (p 165, abstract), which has both a pH-dependent and time-dependent release mechanisms (p 165, ¶ 1 of introduction). The tablet was coated with EUDRAGIT® NE 30D as the inner coating and an outer, pH-dependent coating of EUDRAGIT® FS that degrades specifically in the colon (p 165, ¶ 3 of introduction). No plasticizers were used in the coating of the tablets (p 166, “Materials” and "Coating of

tablets"). A 5.5% coating level for the EUDRAGIT® NE 30D resulted in colon-specific release (p 168), allowing for oral colon-specific drug delivery (p 169).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to prepare a dosage form as described by Ulmius et al. for the treatment of inflammatory bowel diseases using the coating system of Gang et al. The person of ordinary skill in the art would have been motivated to make those modifications to provide colon-specific delivery of the active ingredient following oral administration and reasonably would have expected success because Gang et al. disclose that an dual layer coating of EUDRAGIT® NE 30D and EUDRAGIT® FS results in the colon-specific delivery of active ingredient following oral administration. Such a dosage form would provide the active ingredient to the inflamed colon to exert a local effect, the delivery pattern taught by Ulmius et al. as desirable. Gang et al. teaches that plasticizers and release agents are not required when this combination of polymer layers is used. The placement of the active ingredient can either be in a core, as disclosed by both Ulmius et al. and Gang et al., or in the inner polymeric layer as taught by Ulmius et al. (col 5, ln 5 – 12).

Gang et al. uses the same inner and outer (meth)acrylate copolymers as recited in the instant claims. Therefore, the dosage form must have the same percentage release of active substances in a hypotonic and isotonic release medium as both the cited prior and the instant claims recite dosage forms with the same structure. Dosage forms with the same layers and composition must have the same physical properties, in this case, percentage release of active substance.

(10) Response to Argument

Claims 1 – 3, 8, 9, 13, 14 and 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ulmius et al. (US 5,643,602) in view of Beckert et al. (WO 01/68058, citations from the English equivalent US 2002/019228).

Appellant argues that as shown in the various figures and examples of the instant application release of the active from the pellet is unaffected by the osmotic conditions in the release medium and that the inner methacrylate polymer, e.g., Eudragit® NE30D was responsible for this unexpected effect. Replacement of the Eudragit® NE30D with EUDRAGIT® RL30D, a polymer not encompassed by the claims, displayed differential release depending on the osmotic conditions. The cited art does not teach the selection and arrangement of polymers with the active substance as claimed and certainly does not provide a reasonable expectation for the release criteria defined in the claims. As discussed in greater detail below, these arguments are unpersuasive.

In regards to the Ulmius reference, Appellant argues that nothing in Ulmius provides the necessary direction to specifically select the type of methacrylate polymer from those listed and that such selection to allow release of the active that was not affected by the ionic strength of the dissolution medium could not have been predicted based on the disclosure of Ulmius. These arguments are unpersuasive. The list of polymer for the inner polymer coating provided by Ulmius is a relatively short list and EUDRAGIT® NE is one of 4 preferred film forming polymers (col 5, ln 24 – 27) cited by Ulmius. "[T]he discovery of a previously unappreciated property of a prior art

composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). **MPEP 2112** While Ulmius may not have explicitly appreciated the lack of effect on the release rate in different buffers, the combined prior art teaches a multilayer dosage form having the same structure and composition as recited in the instant claims. As the same compositions must have the same properties, the dosage forms must demonstrate the same release profile, even if such release behavior was not explicitly noted. Further support for this line of argument comes from Knop (Eur J Pharm Sci 1996), who demonstrated that release of theophylline from 'neutral PPMA' coated dosage forms (EUDRAGIT® NE30D was the 'neutral PMMA' material) was independent of the pH and buffer solution composition (Section 2.1, ¶ 4; Section 2.3.1; Section 3.2.5).

Appellant also argue that an 'obvious to try' rationale requires a reasonable expectation of success in order support a conclusion of obviousness and the evidence of record shows that a reasonable expectation of success are not present for the percentage release of active substances. Combinations within the teaching of Ulmius lead to compositions not meeting that definition. These arguments are unpersuasive. Only a reasonable, not an absolute, expectation of success is required to support a conclusion of obviousness. That not all of the inner polymer materials taught by Ulmius

possess the release property recited instant claims does not undermine the reasonable expectation of success in being able to prepare such dosage forms and to select those with the desired properties.

Appellants also argue that with respect to claims 13 – 16 wherein the inner layer is formulated without the aid of excipients such as plasticizers and release agents as is typically the case in such formulations is not at all suggested by Ulmius and/or Beckert. This argument is unpersuasive. Quoting from Ulmius (col 5, ln 49 – 53; emphasis added):

> The coating **may optionally** comprise other pharmaceutically acceptable materials which improve the properties of the film-forming polymers such as plasticizers, antiadhesives [release agents], surfactants and diffusion-accelerating or diffusion-retarding substances.

As these substances are taught as option, formulations without such ingredients are disclosed by the cited prior art.

Appellant also argues that, in essence, the Office fails to understand the role of rebuttal evidence. The Office has dismissed this evidence of unexpected results as "[i]n it's understanding, if it believes that it has made a *prime facie* case of obviousness, no results provided by the invention could possible be unexpected because they flow naturally from following the suggestion of the prior art" (p 11, Appeal Brief). These arguments are unpersuasive. Persuasive rebuttal evidence, for example, would have been found by a showing that single layers of either EUDRAGIT® NE or EUDRAGIT® FS polymers both demonstrated differential release in hypotonic and isotonic release medium but when a combination of these two layers was applied, the release behavior changed and was no longer dependent on the tonicity of the release medium. Based on

the comparisons provided by Appellant, the EUDRAGIT® NE layer alone is sufficient to provide this behavior (¶ 3, p 6 Appeal Brief). The Office has considered the rebuttal evidence presented but did not and does not find the evidence presented persuasive.

Appellant also argues that Beckert teaches away from the claimed invention by placing the active ingredient onto the neutral core and not bound to the inner coating material (which is suggested to EUDRAGIT® RS/RL, which do not work). These arguments are unpersuasive. Ulmius discloses that the non-pareil seed can contain the glucocorticoid or a first layer containing both the glucocorticoid active and polymer (col 5, ln 5 – 20). As mentioned previously, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). (MPEP 2123). Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). **MPEP 2123**, emphasis added. Two alternate arrangements of active ingredient in the primary reference, one being the claimed arrangement, and the use in the secondary reference of the unclaimed arrangement disclosed in the primary reference does not rise to the level of teaching away from the alternate arrangement.

Claims 1 – 3, 8, 9, 13, 14 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ulmius et al. (US 5,643,602) in view of Gang et al. (Proceedings of the 7th SECJ, 2001; cited on IDS submitted July 23, 2009).

Appellant argues this rejection on the grounds that the time dependent release curves of Gang, from a delivery system in which the active ingredient is placed in the core and not bound in the inner methacrylate polymer coating layer as claimed, are different from the release curves of the present invention. In Gang the coating thickness of the inner EUDRAGIT® layer starts the release at different times but then in the same fast manner (delayed burst). Release of active in the present invention in which release is triggered either by the proportion of EUDRAGIT®NE/budesonide or as a function of pH and not as a function of time. These arguments are unpersuasive. First it is noted that other than no more than 10% difference in release between 1 to 5 hours between a hypotonic and isotonic release media, no particular release is recited in the instant claims. The release profiles of Gang as shown in figure 1 was exposed to pH 1.2 simulated gastric fluid for 2 hours and then switched to pH 6.8 simulated intestinal fluid to better simulate the conditions to the which the dosage form would be exposed to upon administration to a human patients. As Eudragit® FS is a pH-dependent polymer that dissolves at higher pH and not lower pH and the data referenced in the instant application showing the pH dependence of the instant invention was carried out in the same pH throughout the duration of the experiment, the difference in release behavior is expected. Appellant have not established that if the release was carried out under the

same conditions and the two dosage forms compared that a difference in behavior would result so the rejection is maintained.

Appellant also argue, as argued above, the role of rebuttal evidence as to providing the unexpected release behavior could not have been predicted. These arguments are unpersuasive. As discussed in greater detail above, the structure of the dosage form determines the release behavior of the dosage form and compositions having the same structure and composition as those claimed is taught by the cited prior art. Appreciation of a new property (e.g., tonicity independent release behavior) does not render an old composition patentably new.

Appellant lastly argues that nothing in Ulmius and Gang provides the necessary direction in polymer selection. This argument is unpersuasive. Gang teaches the exact combination of polymers – an inner coating of EUDRAGIT® NE with an outer coating of EUDRAGIT® FS – although the location of the active ingredient is different. Ulmius (col 5, ln 5 – 20) discloses that the active ingredient can be placed in the core or in the inner layer. In the light of this explicitly taught combination of polymers, no additional guidance from Ulmius to select those polymers is required.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Nissa M Westerberg/

Examiner, Art Unit 1618

Conferees:

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612